

REMARKS

Reconsideration is requested.

Claims 10, 12-23 and 26-38 are pending. Claims 22, 23, 37 and 38 have been withdrawn from consideration. Rejoinder and allowance of any claim defining a method of making and/or using a product defined by an allowable claim, at an appropriate time, are requested.

Claim 12 has been revised, without prejudice to define the stated alternative in a more traditional U.S. claim format. Claim 26 has been revised, without prejudice, to refer to the components involved in NHR described, for example, on page 14, lines 12-30 of the specification. Claim 27 has been revised, without prejudice, to refer to alternatives in a more traditional U.S. claim format. Claims 29 and 30 have been revised, without prejudice, to refer to alternatives in the unamended claim 32. Claim 32 has been revised, without prejudice, to remove the alternatives, as is more traditional in U.S. claim practice. No new matter has been added. The amendments do not add new claims and do not raise new issues requiring further search and/or consideration. Entry of the present Amendment is requested.

The Section 112, first paragraph "written description", rejection of claims 10, 12-21 and 26-36 is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following and the attached.

The Examiner is urged to appreciate that the applicants are not required to describe in their specification that which is known. A patent specification is directed to one of ordinary skill in the art.

The Examiner is understood to believe that adequate written description of the claimed subject matter requires that particular nucleic acid

“an actual reduction to practice of the claimed filamentous fungus, *Aspergillus*, *Penicillium* *Trichoderma*, *Aspergillus oryzae*, or *Penicillium citrinum* cells because the specification fails to disclose the structure of *hdfA* and *hdfB* (or their homologs) genes in non-Aspergillus niger and *Penicillium chrysogenum*,” see pages 4-5 of the Office Action dated December 24, 2009.

The Examiner further asserts that

“The level of knowledge and skill in the art does not allow those skilled in the art to structurally envisage or recognize any or all filamentous fungus, any or all *Aspergillus*, any or all *Penicillium*, any or all *Trichoderma*, *Aspergillus oryzae*, or *Penicillium citrinum* having a deletion or mutation of its *hdfA*, *hdfB* or homologs thereof or increased level of a component involved in HR because it is known that corresponding genes in different species tend to differ in sequence and the amount and type of sequence variation is unpredictable.”
See page 5 of the Office Action dated December 24, 2009.

The Examiner’s characterization of the level of ordinary skill in the art is contrary to the characterization provided in the attached Carvalho et al (“Expanding the *ku70* toolbox for filamentous fungi: establishment of complementation vectors in recipient strains for advanced gene analyses” Applied Genetics and Molecular Biotechnology, Published online 27 April 2010 (DOI 10.1007/s00253-010-2588-1)) wherein the authors note the following:

“When Ninomiya et al. (2004)^[1] reported that inactivation of components of the non-homologous end-joining (NHEJ) pathway in *Neurospora crassa* results in strains with homologous recombination frequencies up to 100%, this system was rapidly established in other filamentous fungi

¹ Published August 17, 2004, of record and published after the April 2, 2004 filing of the presently-claimed priority EP 04076057.1

(for reviews see (Meyer 2008, Kück and Hoff 2010)).” See Introduction, first paragraph.

Carvalho et al therefore confirm that, as of 2004, one of ordinary skill in the art was able to apply the specific direction of Ninomiya (2004) to “other filamentous fungi”.

Ninomiya (2004) demonstrated that

“exogenous DNA is integrated into homologous sequences in the genome of *N. crassa* at a frequency of 100% in *mus-51* and *mus-52* strains, indicating that suppression of NHEJ increases the frequency of HR. This finding has strong implications for recombination technology, because it is easy to make genetic alterations in the *mus-51* or *mus-52* mutants as recipients for transformation, and because these mutants do not show severe defects, but differ from wild type only in being moderately sensitive to mutagens that produce double strand breaks.” See Discussion.

Ninomiya (2004) concluded, as appears to have been confirmed by Carvalho et al, that

“Our findings with *Neurospora* change this situation [i.e., the previous inability to efficiently knock out targeted genes in eukaryotes]. They should be widely applicable to other systems.” Id. (emphasis added).

Not surprisingly, similar results were reported by Nayak et al (“A versatile and efficient gene-targeting system for *Aspergillus nidulans*” Genetics 172: 15557-1566 (March 2006) (copy attached)). Nayak (2006) reports in the attached that

“The filamentous fungus *Aspergillus nidulans* is an important experimental organism. Significant findings in a number of areas have resulted from work with *A. nidulans*, and it serves as an important model organism for the genus *Aspergillus*, which includes commercially important fermentation organisms as well as serious pathogens.” See page 1557, left hand column.

“Our approach is based on the results of Ninomiya et al. (2004) who found that the deletion of genes required for nonhomologous end joining DNA repair (homologs of the human KU70 and KU80 genes) increases the frequency of gene replacement in *Neurospora crassa*. We have identified

and deleted the *A. nidulans* KU70 homolog.” See page 1557, right hand column.

Nayak (2006) therefore was able to extend the specific teachings of Ninomiya (2004) to identify and delete the *A. nidulans* KU70 homolog. Nayak (2006) and Ninomiya (2004) demonstrate therefore that the level of skill in the art was greater than that described by the present Examiner and that the specific description of a species, such as is provided by Ninomiya (2004) was extended by application of the generally advanced level of skill in the art to locate homologous sequences in other filamentous fungi.

Nayak (2006) concludes that

“While there will certainly be variations among organisms, our data, in combination with the data of Ninomiya et al. (2004), suggest that deletion of KU homologs may be a generally useful strategy for improving gene targeting.” See page 1565, left hand column of Nayak (2006).

Further evidence of the applicability of the claimed method is found in the attached Choi et al (“Enhanced Homologous Recombination in *Fusarium verticillioides* by Disruption of *FvKU70*, a Gene Required for a Non-homologous End Joining Mechanism” Plant Pathol. J. 24(1): 1-7 (2008)) which describes that

“In filamentous fungi, homologous recombination (HR) is primarily utilized for generating targeted gene replacement mutants, and in *F. verticillioides*, like other fungi, HR frequency is quite low (<2%) (Weld et al., 2006).”

...

“Recent reports demonstrate drastic improvement in HR frequency in filamentous fungi by disrupting Ku70 or Ku80 (Goin et al., 2006; Haarmann et al., 2008; Krappmann et al., 2006; Meyer et al., 2007; Nayak et al., 2006; Ninomiya et al., 2004; Ueno et al., 2007). In this study, we hypothesized that *F. verticillioides* HR frequency can be improved by disrupting the NHEJ mechanism. To test this hypothesis, we generated

a gene deletion mutant of *F. verticillioides* KU70 homolog (FvKU70) and analyzed HR frequency in the mutant strain (SF41). We also investigated the impact of FvKU70 deletion on key *F. verticillioides* phenotypes, e.g., development, secondary metabolism, and virulence, in SF41.” See pages 1-2 of Choi et al.

Choi et al therefore confirm that a number of authors were able to apply the discovery of the presently claimed invention to “demonstrate drastic improvement in HR frequency in filamentous fungi by disrupting Ku70 of Ku80.” Choi et al summarized their findings as follows:

“In summary, we demonstrated that HR frequency in *F. verticillioides* can be improved significantly by using a nonhomologous end-joining-deficient mutant strain SF41. Published reports show that HR frequency of 70-100% can occur in other filamentous fungi, e.g., *N. crassa*, *Aspergillus fumigatus*, *A. nidulans*, *Cryptococcus neoformans*, *Sordaria macrospora*, and *Magnaporthe grisea* (Goin et al., 2006; Krappmann et al., 2006; Nayak et al., 2006; Ninomiya et al., 2004; Villalba et al., 2008). While the level of HR frequency was not as high as these filamentous fungi, increased HR frequency in SF41 is a drastic improvement from that of wild type.” See page 5 of Choi et al.

One of ordinary skill in the art will appreciate that the applicants were in possession of the claimed invention at the time the application was filed.

The Examiner suggests that the written description requirement of Section 112, requires an actual reduction to practice and identification of specific sequences. The Examiner provides no support for such a requirement. The applicants submit, with due respect, that the Examiner’s apparent requirement for a greater amount of written description in the filed specification is improper and inconsistent with the written

description requirement as described recently by the court in Capon v. Eshhar, 418 F.3d 1349; 76 USPQ2d 1078 (Fed. Cir. 2005).

An application contains adequate written description of the claimed subject matter if the disclosure of that patent application conveys with reasonable clarity to those skilled in the art that Appellants were in possession of the claimed invention at the time the application was filed. Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555; 19 USPQ2d 1111 (Fed. Cir. 1991). Possession of the invention can be shown by "describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention." (MPEP § 2163.) The description need only describe in detail that which is not new or not conventional. (Id.) "An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Id. (citations omitted).

The Federal Circuit in Capon commented that precedent indicates that compliance with the written description requirement for generic claims to biological subject matter should be reviewed in view of the existing knowledge in the field, the prior art, the maturity of the technology, the predictability of the aspect at issue and other appropriate considerations. Id. at 1359.

Similarly, the Federal Circuit in Falkner v. Inglis, 448 F.3d 1357 (Fed. Cir. 2006) stated that the written description requirement does not require the recitation or incorporation by reference of genes and sequences when this information is available in accessible literature sources at the relevant date. Id. at 1367, citing, Capon v. Eshhar, 418 F. 3d 1349 (Fed. Cir. 2005). The Falkner court held that "(1) examples are not necessary to support the adequacy of a written description (2) the written description standard may be met (as it is here) even where actual reduction to practice of an invention is absent; and (3) there is no per se rule that an adequate written description of an invention that involves a biological macro-molecule must contain a recitation of known structure." Falkner at 1365.

The claims are supported by an adequate written description. One of ordinary skill in the art will appreciate that the applicants were in possession of the claimed invention at the time the application was filed. Withdrawal of the Section 112, first paragraph "written description" rejection is requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested. The Examiner is requested to contact the undersigned, preferably by telephone, in the event anything further is required.

DEKKER et al.
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Respectfully submitted,

NIXON & VANDERHYE P.C.

By: /B. J. Sadoff/
 B. J. Sadoff
 Reg. No. 36,663

BJS:
901 North Glebe Road, 11th Floor
Arlington, VA 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100